AT

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,753	03/14/2001	Erwin W. Gelfand	2879-74	5001

22442 7590 04/21/2004

SHERIDAN ROSS PC
1560 BROADWAY
SUITE 1200
DENVER, CO 80202

EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/809,753	GELFAND ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,12-14,20-30,38-40 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,12-14,20-30,38-40 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/1/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/12/04 has been entered.

2. Claims 1, 3-10, 12-14, 20-30, 38-40 and 42 are pending and are being acted upon in this Office Action.

3. The declaration filed by Erwin W. Gelfand and Azzeddline Dakhama filed on 2/12/04 under 37 CFR 1.131 in anticipation of a 102(e) rejection from the 2002/0037846A1 reference has been considered. However, it is premature to file such declaration since no patent has been issued from the U.S. patent application 2002/0037846A1 and no rejection has been made under 35 USC 102(e) using the issued patent. Further, an affidavit or declaration is inappropriate under 37 CFR 1.131(a) when the reference is claiming the same patentable invention, see MPEP § 2306. If the reference and this application are not commonly owned, the reference can only be overcome by establishing priority of invention through interference proceedings. See MPEP Chapter 2300 for information on initiating interference proceedings. If the reference and this application are commonly owned, the patent may be disqualified as prior art by an affidavit or declaration under 37 CFR 1.130. See MPEP § 718.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3-10, 12-14, 20-30, 38-40 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal comprising administering to a mammal a human calcitonin gene related peptide (CGRP) wherein said mammal has or is at risk of developing, airway hyperresponsiveness, **does not** reasonably provide enablement for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal comprising administering to said mammal any calcitonin gene related peptide (CGRP), any "fragment of any CGRP" with any CGRP biological activity, and any "homologue of any CGRP with any CGRP biological activity as set forth in claims 1, 3-10, 12-14, 20-26, 29-30, 38-40 and 42 in conjunction with *any* "CGRP receptor activity modified protein (RAMP)" in claim 28 or *any* other β-agonists (long or short acting), *any* leukotriene modifiers such as any (inhibitors or receptor antagonist), or *any* "phosphodiesterase inhibitors" as set forth in claim 27. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method to inhibit airway hyperresponsiveness (AHR) in mice sensitized to ovalbumin by administering only human αCGRP (page 61, in particular). The inhibition of AHR can be block by a CGRP antagonist (8-37 residues of the full-length αCGRP protein), which is a fragment of CGRP. The specification defines the term "CGRP receptor agonist" on page 25 as any compound, any agent, including but not limited to antibody, CGRP homologue, any suitable product of drug design such as mimetic of CGRP. The specification on page 28, line 12-13, defines a CGRP protein includes protein homologues or mimetic of CGRP; the term "homologue" is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but limited

to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification).

The specification does not teach how to make, much less how to use *any* CGRP, any fragment of any CGRP with which CGRP activity, and any CGRP homolog with which CGRP activity for a method to inhibit airway hyperresponsiveness in a mammal induced by allergen because the terms "homolog", "fragment" and "CGRP" without the amino acid sequence have no structure. Further, the "homologue" as defined in instant specification is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but not limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification). However, there is insufficient guidance as to which amino acids within all GCRP to be added, deleted, substitute for which amino acids and whether the resulting CGRP homologue maintains the same function as CGRP, in turn, would be useful for inhibit airway hyperresponsiveness sensitized by allergen.

Zhu *et al* (PTO 1449) teach calcitonin gene-related peptide (CGRP) may play different physiological and pathophysiological roles in airway regulation in different species such as horse, human Sprague-Dawley rat, and mouse (See Discussion, in particular).

Kanazawa *et al* teach a CGRP fragment such as CGRP8-37. Although the reference CGRP fragment binds to the CGRP receptor, it has antagonistic activity to CGRP (see abstract, in particular). Kanazawa et al further teach CGRP homolog such as adrenomedullin (AM) that has 50% sequence identity to CGRP. While the reference CGRP homolog inhibits histamine induced bronchoconstriction in a dose dependent manner, the CGRP or the CGRP fragment CGRP8-37 alone did not affect pulmonary resistance. Further, pretreatment with CGRP or the CGRP fragment CGRP8-37 did not significantly affect histamine-induced bronchoconstriction (See abstract, in particular). Given the indefinite number of undisclosed "homolog", and "CGRP fragment" that bind to more than one CGRP receptors and mediate different "CGRP biological activity", there is insufficient in vivo working example demonstrating that all CGRP fragment, all homologue and all CGRP are effective for the claimed method of inhibiting allergen-induced airway hyperresponsiveness. Other than human CGRP, it is unpredictable which undisclosed "homolog", and "CGRP fragment" are effective for inhibiting allergen induced airway hyperresponsiveness. Until the specific homolog, CGRP fragment, and mimetic have been identified and have the specific CGRP biological activity, the disclosure merely invites one of skill in the art for further experimentation.

With regard to "CGRP receptor activity modified protein (RAMP)" in claim 28 and *any* other β-agonists (long or short acting), *any* leukotriene modifiers such as any (inhibitors or receptor antagonist), or *any* "phosphodiesterase inhibitors" as set forth in claim 27, in addition to the problem of CGRP fragment and CGRP homolog in the claimed method, the term "CGRP receptor activity modified protein" without the amino acid sequence has no structure. The terms "β-agonists", "leukotriene modifiers" and "phosphodiesterase inhibitors" without the chemical structure have no structure, let alone how to make and use such as compound in the claimed method.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities. Given the indefinite number of "CGRP receptor activity modified protein (RAMP)", "β-agonists", "leukotriene modifiers" and "phosphodiesterase inhibitors" and the lack of sufficient in vivo working example, it is unpredictable which undisclosed "CGRP receptor activity modified protein (RAMP)", "β-agonists", "leukotriene modifiers" and "phosphodiesterase inhibitors" in conjunction with which CGRP, CGRP fragment or CGRP homolog is efficacious for a method to inhibit allergen-induced airway hyperresponsiveness in all mammal.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 2/14/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claims have been amended to recite the simplified list of CGRP agents of: CGRP, a fragment of CGRP having biological activity, and a homologues of CGRP having biological activity. (2) a demonstration that a fragment or homologue of CGRP has similar biological activity to the native peptide, regardless of the standard used to compare two moieties, is sufficient to provide at least a reasonable expectation that biologically active fragment or homologue will operate in a similar manner to the native peptide. (3) The present specification teaches nucleic acid and amino acid sequences for CGRP from a variety of mammalian species (page 27, lines 9-14). (4) The homology of CGRP among species is very high and the working examples of the specification show that mouse and human CGRP peptides can be used interchangeably (example 3). (5) amino acid positions 8-37 has an antagonist function. (6) Various agonist homologues of CGRP are known in the art (page 34, line 27 to page 35, line 5). (7) The study of Zhu et al is directed primarily to the effect of capsaicin on sensory nerve fibers and they conclude that sensory neuropeptides such as SP or CGRP released from capsaicin-sensitive nerves have no direct effect on smooth muscle tone.

In response, amended claim 1 still recite a method ...calcitonin gene related peptide (CGRP), a fragment of CGRP with CGRP biological activity, and a homologue of CGRP with CGRP biological activity...mammal. The scope of the claims encompasses a method to inhibit allergen-induced airway hyperresponsiveness comprising administering a genus of calcitonin gene related peptide (CGRP), fragment and homolog thereof. The specification discloses only a method to inhibit airway hyperresponsiveness (AHR) in mice sensitized to ovalbumin by administering only human αCGRP (page 61, in particular). The specification does not define the specific CGRP biological activity. The specification does not teach how to make *any* CGRP, any fragment of any CGRP with which CGRP activity, and any CGRP homolog with which CGRP activity, let alone for a method to inhibit airway hyperresponsiveness in a mammal induced by allergen because the terms "homolog", "fragment" and "CGRP" without the amino acid sequence have no structure. Further, the term "homologue" is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but not limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification). However, there is insufficient guidance as to which amino acids within the full-length of all GCRP to be added,

deleted, substitute for which amino acids and whether the resulting CGRP homologue maintains the same function as CGRP, in turn, would be useful for inhibit airway hyperresponsiveness sensitized by allergen.

Zhu *et al* (PTO 1449) teach calcitonin gene-related peptide (CGRP) may play different physiological and pathophysiological roles in airway regulation in different species such as horse, human Sprague-Dawley rat, and mouse (See Discussion, in particular).

Kanazawa *et al* teach a CGRP fragment such as CGRP8-37. Although the reference CGRP fragment binds to the CGRP receptor, it has antagonistic activity to CGRP (see abstract, in particular). Kanazawa et al further teach CGRP homolog such as adrenomedullin (AM) that has 50% sequence identity to CGRP. While the reference CGRP homolog inhibits histamine induced bronchoconstriction in a dose dependent manner, the CGRP or the CGRP fragment CGRP8-37 alone did not affect pulmonary resistance and pretreatment with CGRP or the CGRP fragment CGRP8-37 did not significantly affect histamine-induced bronchoconstriction (See abstract, in particular).

Given the indefinite number of undisclosed "homolog", and "CGRP fragment" that bind to more than one CGRP receptors and mediate different "CGRP biological activity", there is insufficient in vivo working example demonstrating that all CGRP fragment, all homologue and all CGRP are effective for the claimed method of inhibiting allergen-induced airway hyperresponsiveness. Other than human CGRP, it is unpredictable which undisclosed "homolog", and "CGRP fragment" are effective for inhibiting allergen induced airway hyperresponsiveness. Until the specific homolog, CGRP fragment, and mimetic have been identified with the specific CGRP biological activity, the disclosure merely invites one of skill in the art for further experimentation.

6. Claims 1, 3-10, 12-14, 20-30, 38-40 and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal comprising administering to said mammal any calcitonin gene related peptide (CGRP), any "fragment of any CGRP" with any CGRP biological activity, any "homologue of any CGRP with any CGRP biological activity as

set forth in claims 1, 3-10, 12-14, 20-26, 29-30, 38-40 and 42 in conjunction with any CGRP receptor activity modified protein (RAMP) in claim 28 or any other β-agonists (long or short acting), any leukotriene modifiers such as any (inhibitors or receptor antagonist), any phosphodiesterase inhibitors as set forth in claim 27.

The specification discloses only a method to inhibit airway hyperresponsiveness (AHR) in mice sensitized to ovalbumin by administering only human αCGRP (page 61, in particular). The inhibition of AHR can be block by a CGRP antagonist (8-37 residues of the full-length αCGRP protein), which is a fragment of CGRP. The specification defines the term "CGRP receptor agonist" on page 25 as any compound, any agent, including but not limited to antibody, CGRP homologue, any suitable product of drug design such as mimetic of CGRP. The specification on page 28, line 12-13, defines a CGRP protein includes protein homologues or mimetic of CGRP; the term "homologue" is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification).

Other than the specific human CGRP that binds to the αCGRP receptor for the claimed method of inhibiting allergen-induced airway hyperresponsiveness, there is inadequate written description about the structure associated with function of all CGRP agent such as all CGRP, all fragment of all CGRP, all homolog of CGRP, all CGRP receptor activity modified protein (RAMP), all β-agonists (long or short acting), all leukotriene modifiers such as any (inhibitors or receptor antagonist), and all phosphodiesterase inhibitors for a method of inhibiting allergen-induced airway hyperresponsiveness in all mammal. The terms "CGRP", "fragment", "homolog", "RAMP", "agonist", "antagonist" and "inhibitors" without the amino acid sequence or chemical structure have no structure, much less function. Further, the "homologue" as defined in instant specification is referred to any peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but not limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification). However, there is inadequate written description about which amino acids within the full-length of all GCRP to be added, deleted, substitute for which amino acids. Other than the human CGRP, all the CGRP, fragment and homologue thereof for the claimed method are not adequately described.

The specification discloses only one specific human and mouse CGRP for the claimed method. Given the lack of a written description of *any* additional representative species of CGRP, CGRP fragment, and homolog of CGRP, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 2/12/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claims have been amended to recite the simplified list of CGRP agents of: CGRP, a fragment of CGRP having biological activity, and a homologues of CGRP having biological activity. (2) The present specification teaches nucleic acid and amino acid sequences for CGRP from a variety of mammalian species (page 27, lines 9-14). (3) The homology of CGRP among species is very high and the working examples of the specification show that mouse and human CGRP peptides can be used interchangeably (example 3). (4) Amino acid positions 8-37 of CGRP has an antagonist function. (5) Various agonist homologues of CGRP are known in the art (page 34, line 27 to page 35, line 5). (6) The specification provides a teaching of a homologue that does not have CGRP biological activity. (7) The specification provides the specific definitions of such agent and several references to the known structure of the native CGRP peptides as well as to various homologues thereof.

In response, amended claim 1 still recite a method ...calcitonin gene related peptide (CGRP), a fragment of CGRP with CGRP biological activity, and a homologue of CGRP with CGRP biological activity...mammal. The scope of the claims encompasses a method to inhibit allergen-induced airway hyperresponsiveness comprising administering a genus of calcitonin gene related peptide (CGRP), fragment and homolog thereof. The specification discloses only a method to inhibit airway hyperresponsiveness (AHR) in mice sensitized to ovalbumin by administering only human αCGRP (page 61, in particular). The inhibition of AHR can be block by a CGRP antagonist (8-37 residues of the full-length αCGRP protein), which is a fragment of CGRP. The specification defines the term "CGRP receptor agonist" on page 25 as any

compound, any agent, including but not limited to antibody, CGRP homologue, any suitable product of drug design such as mimetic of CGRP. The specification on page 28, line 12-13, defines a CGRP protein includes protein homologues or mimetic of CGRP; the term "homologue" is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification). Other than the specific human CGRP that binds to the αCGRP receptor for the claimed method of inhibiting allergen-induced airway hyperresponsiveness, there is inadequate written description about the structure associated with function of all CGRP agent such as all CGRP, all fragment of all CGRP, and all homolog of CGRP for a method of inhibiting allergen-induced airway hyperresponsiveness in all mammal. The terms "CGRP", "fragment" and "homolog" without the amino acid sequence has no structure, much less which CGRP biological activity. Further, the "homologue" as defined in instant specification is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but not limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification). However, there is inadequate written description about which amino acids within the full-length of all GCRP to be added, deleted, substitute for which amino acids. Other than the specific CGRP for the claimed method, the other CGRP, fragment and homologue thereof for the claimed method are not adequately described.

The specification discloses only one specific human CGRP for the claimed method. Given the lack of a written description of *any* additional representative species of CGRP fragment, and homolog of CGRP, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 3-5, 8-9, 12, 20-21, 23, 25-26, 29, 38, and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Cadieux *et al* (of record, Am J Respir Crit Care Med 159: 235-243, Jan 1999; PTO 892).

Cadieux *et al* teach a method of inhibiting allergen induced airway hyperresponsiveness in a mammal comprising administering to a mammal such as guinea pigs a CGRP agent such as calcitonin gene related peptide (CGRP) wherein the reference mammal has been sensitized to an allergen such as ovalbumin (See entire document, Methods, Figure 2, page 237, column 2, page 241, column 2, third paragraph, in particular). The reference agent is administered at a dose of 0.38 μg/ kg body weights, which is about 0.1 to about 20 μg/kg body weight (See page 237, column 1, 5th paragraph, in particular). Cadieux *et al* teach that pretreatment of CGRP at various concentrations such as 10^{-9} to 10^{-6} M, which is about 0.1 μg/ kg body weight to about 10 or 5 about μg/ kg body weight of the reference mammal (See page 238, column 2, 1st paragraph, in particular). The term "about" expands the claimed range to include the reference concentration. The reference CGRP inherently binds to and activates a CGRP receptor in the lungs of the reference mammal. Claims 5 and 8-9 are included in this rejection because the reference teaches administering CGRP five minutes prior challenge and this step is repeated, and five minutes is within 12 hours, 2 hours or between 48 hours or less prior to exposure to AHR provoking stimulus. Claim 25 is included in this rejection because the reduction of airway hyperresponsiveness such that the FEV1 value is improved by at least about 5% is inherent properties of the reference CGRP and properties of CGRP cannot be separate from the compound. The reference agent is targeted to cells in the lung such as smooth muscle cells and epithelial cells (See page 241, column 1, line 2nd paragraph, in particular). The reference agent is administered by intravenous injection or by direct delivery to the lung in the organ bath of the reference mammal (See Chemicals and Solutions, caption of Figure 2, page 236, column 2, 2nd paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 6-7, 10, 22, 24, 27, 30, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cadieux *et al* (or record, Am J Respir Crit Care Med 159: 235-243, Jan 1999; PTO 892) in view of US Pat No. 5,858,978 (of record, Jan 1999; PTO 1449) or US Pat No. 5,635,478 (of record, June 1997; PTO 1449).

The teachings of Cadieux *et al* have been discussed supra. Cadieux *et al* further teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

The claimed invention in claim 6 differs from the teachings of the reference only that the method wherein the agent is administered upon the detection of the first symptoms of AHR.

The claimed invention in claim 7 differs from the teachings of the references only that the method wherein the agent is administered within one hour after the detection of the first symptoms of AHR.

The claimed invention in claim 10 differs from the teachings of the reference only that the method wherein the agent is administered every one to two days.

The claimed invention in claim 22 differs from the teachings of the reference only that the method wherein the agent is administered by aerosol delivery.

The claimed invention in claim 24 differs from the teachings of the reference only that the method wherein the agent is administered by oral delivery.

The claimed invention in claim 27 differs from the teachings of the reference only that the method wherein the agent is administered to said mammal in conjunction with another agent such as corticosteroids (oral or injected), or phosphodiesterase inhibitor.

The claimed invention in claim 30 differs from the teachings of the reference only that the method wherein the mammal is a human.

The claimed invention in claim 40 differs from the teachings of the reference only that the method wherein the agent is a homologue of CGRP.

The '978 patent teaches a method of using agent such as calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat for a method of inhibiting acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness due to constriction, in human (See column 5, lines 12-13, column 7, lines 45-49, claims of '978 patent, in particular). The reference agents are administered into the respiratory tract such as the lung by aerosol spray (See column 7, lines 45-49, in particular) or administered orally such as tablet or sublingual (See column 6, lines 3-7, in particular). The '978 patent teaches the reference method is useful in treatment of a variety of acute and chronic inflammatory respiratory disorders by administering CGRP alone and in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor conventionally used to treat such diseases (See column 5, lines 36-39, lines 47-53, in particular). The '978 patent teaches the reference pharmaceutical composition comprises an effective unit dosage at a concentration effective to evoke the desired response by the route appropriate for the particular pharmaceutical carrier (See column 7, lines 6-61, in particular). The '978 patent teaches that the reference agents are administered in multiple successive dosages, spaced as frequently as 6-12 hours apart or as long as six weeks until symptomatic relief is obtained (See column 7, lines 50-55, in particular) or every 24 hours or longer (See column 7, lines 35, in particular).

The '478 patent teaches a method of using agent such as calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat for a method of inhibiting acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness in human (See column 13, lines 1-6, column 2, lines 39-66 column 3, lines 1-8, in particular). The reference agents are administered into the respiratory tract such as the lung by aerosol spray (See column 6, lines 35, in particular) or administered orally (See column 7, line 3, in particular) or administered by parenterally (See column 6, lines 37-38, in particular). The '478 patent teaches the reference agents are useful in treatment of a variety of acute and chronic inflammatory respiratory disorders, by administering CGRP alone or in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor which conventionally used to treat such diseases (See column 5, lines 36-39, lines 47-53, in particular). The '478 patent teaches the pharmaceutical composition comprises an effective unit dosage at a concentration effective to evoke the desired response by the route appropriate for

the particular pharmaceutical carrier (See column 6, lines 60-67 bridging column 7, lines 1-10, in particular). The '478 patent teaches the reference agents is administered in multiple successive dosages, spaced as frequently as 6-12 hours apart or as long as six weeks until symptomatic relief is obtained (See column 7, lines 37-51, in particular). Claim 3 is included in this rejection because asthma induced airway hyperresponsiveness is due to inhalation or exposure to allergen. Claim 6 is included in this rejection because the references teach the reference agents are administered to ameliorate the symptoms associated with asthma. Claims 7 and 9 are included in this rejection because the '978 patent teaches administering CGRP to inhibit acute inflammation disorder such as asthma and the recitation of administering within 1 hour after the detection of the first symptoms of AHR or administered within 2 hours or less is within the purview of one skill in the art at the time the invention was made to intervene by administering CGRP as taught by the '978 and the '478 patents.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the CGRP as taught by the Cadieux *et al* for the homolog of CGRP that binds to and activate CGRP receptor or combine the CGRP as taught by Cadieux with another agent such as corticosteroids or phosphodiesterase inhibitor as taught by either the '978 patent or the '478 patent for a method of to inhibit allergen-induced airway hyperresponsiveness in a mammal as taught by Cadieux *et al* and the '978 patent or the '478 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '978 patent teaches that the CGRP and homologue thereof are useful for treating a variety of acute and chronic inflammatory respiratory disorders by administering CGRP alone and in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor conventionally used to treat chronic inflammatory respiratory disorders (See column 5, lines 36-39, lines 47-53, in particular). The '478 patent teaches that the reference agents are useful in treatment of a variety of acute and chronic inflammatory respiratory disorders, by administering CGRP or homologue thereof alone or in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor which conventionally used to treat such diseases (See column 5, lines 36-39, lines 47-53, in particular). Cadieux *et al* teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of

airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, abstract, in particular).

12. Claims 1, 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cadieux *et al* (of record, Am J Respir Crit Care Med 159: 235-243, Jan 1999; PTO 892) in view of Suissa *et al* (of record, Ann Intern Med 126(3): 177-83, Feb 1997; PTO 892).

The teachings of Cadieux *et al* have been discussed supra. Cadieux *et al* further teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

The claimed invention as recited in claim 25 differs from the teachings of the reference only that the agent reduces the airway hyperresponsiveness of the mammal such that the FEV1 value of said mammal is improved by at least about 5%.

The claimed invention as recited in claim 27 differs from the teachings of the reference only that the agent is a leukotriene modifiers such as receptor antagonist and β-agonists (along or short acting).

Suissa *et al* teach a combination of leukotriene receptor antagonist such as zafirluast and beta agonist treatment is more effective than beta-agonist alone in treating mild-to-moderate asthma (See abstract, in particular). Suissa *et al* teach patients with mild-to-moderate asthma have a decrease in forced expiratory volume in 1 s (FEV1) which at least 55% of the predicted value and these patients have reduced airway hyperresponsiveness. The reference leukotriene receptor antagonist zafirlukast alone improves bronchial hyperresponsiveness by 89%, which is at least 5% improvement (See entire document, abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the leukotriene receptor antagonist or beta agonist as taught by Suissa *et al* with the Calcitonin Gene-related peptide (CGRP) as taught by Cadieux *et al* for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal as taught by Cadieux *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Suissa *et al* teach any combination of leukotriene receptor antagonist and beta agonist treatment is more

effective than beta-agonist alone in treating mild-to-moderate asthma (See abstract, in particular) and zafirlukast alone improves bronchial hyperresponsiveness by 89%, which is at least 5% improvement (See entire document, abstract, in particular). Cadieux *et al* teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limiting the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

13. Claims 1 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cadieux *et al* (of record, Am J Respir Crit Care Med 159: 235-243, Jan 1999; PTO 892) in view of Drazen *et al* (of record, Am J Respir Crit Care Med 157(2): S233-7, June 1998; PTO 892) or Abraham *et al* (of record, Pulm Pharmacol 11(4): 271-6, June 1998; PTO 892) or Abdelaziz *et al* (Eur Respir J 10(4): 851-7; April 1997; PTO 892) or Barnes *et al* (of record, Eur Respir J 7(3): 579-91, March 1994; PTO 892) or Hoshino *et al* (of record, Allergy 52(8): 814-20, Aug 1997; PTO 892).

The teachings of Cadieux *et al* have been discussed supra. Cadieux *et al* further teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

The claimed invention as recited in claim 27 differs from the teachings of the reference only that the method wherein the agent is administered to a mammal in conjunction with another agent selected from the group consisting of β-agonists, leukotriene modifiers (inhibitors or receptor antagonists), antihistamines, sodium cromoglycate, nedocrimal and theophylline.

Drazen *et al* teach leukotriene receptor antagonist such as (cysteinyl leukotriene (cysLT) and zafirlukast and 5-lipoxygenase (5-LO) inhibitor such as zileuton are safe and effective asthma treatment that improve pulmonary function and reduce airway inflammation, including inflammatory cell counts and airway hyperresponsiveness (See abstract, in particular).

Abraham *et al* teach agents such as cromolyn sodium (disodium cromoglycate) and beta 2 mimetic reproterol hydrochloride and the combination gives better protection against post-antigen-induced airway hyperresponsiveness (AHR) than either one alone (See abstract, in particular).

Abdelaziz *et al* teach agent such as nedocromil sodium can reduce airway hyperresponsiveness by inhibiting eosinophil chemotaxis and adherence induced by human bronchial cell derived mediators (See abstract, in particular).

Barnes *et al* teach agent such as theophylline for treatment of asthma and is widely use as a bronchodilator that has anti-inflammatory activities such as inhibiting cytokines synthesis and release, as well as airway hyperresponsiveness (See abstract, in particular).

Hoshino *et al* teach an agent such as Ketotifen, which is an antihistamine. Ketotifen is beneficial for inhibiting activated eosinophils and T cell infiltration of inflammatory cells into the airway associated with asthma.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the leukotriene receptor antagonist and 5-lipoxygenase (5-LO) inhibitor as taught by Drazen *et al* or the cromolyn sodium as taught by Abraham *et al* or the nedocromil sodium as taught by Abdelaziz *et al* or the theophylline as taught by Barnes *et al* or the anti-histamine as taught by Hoshino *et al* with the Calcitonin Gene-related peptide (CGRP) for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal as taught by Cadieux *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Drazen *et al* teach that any leukotriene receptor antagonist and any 5-lipoxygenase (5-LO) inhibitors are effective for asthma since it improves pulmonary function and reduces airway inflammation, including inflammatory cell counts and airway hyperresponsiveness (See abstract, in particular). Abraham *et al* teach cromolyn sodium (disodium cromoglycate) and beta 2 mimetic reproterol hydrochloride in combination gives better protection against post-antigen-induced airway hyperresponsiveness (AHR) than either one alone (See abstract, in particular). Abdelaziz *et al* teach that nedocromil sodium can reduce airway hyperresponsiveness by inhibiting eosinophil chemotaxis and adherence induced by human bronchial cell derived mediators (See abstract, in particular). Barnes *et al* teach that theophylline is useful as a bronchodilator and has anti-inflammatory activities such as inhibiting cytokines synthesis and release, including airway hyperresponsiveness (See abstract, in particular). Hoshino *et al* teach that antihistamine is beneficial for inhibiting activated eosinophils and T cell infiltration of inflammatory cells into the airway associated with asthma. Cadieux *et al* teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

14. Claims 1, 28 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cadieux *et al* (of record, Am J Respir Crit Care Med 159: 235-243, Jan 1999; PTO 892) in view of WO 98/03534 publication (January 1998; PTO 1449).

The teachings of Cadieux *et al* have been discussed supra. Cadieux *et al* further teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

The claimed invention in claim 28 differs from the teachings of the reference only that the agent is administered to said mammal in conjunction with a CGRP receptor activity modified protein (RAMP).

The claimed invention as recited in claim 39 differs from the teachings of the reference only that the agent is a fragment of CGRP that binds to and activates a CGRP receptor.

The claimed invention as recited in claim 41 differs from the teachings of the reference only that the agent is a CGRP analog that binds to and activates a CGRP receptor.

The WO 98/03543 publication teaches various calcitonin gene-related peptide agonist such as CGRP-RCF analog and fragment thereof that binds to the CGRP receptor and retains essentially the same biological function as a human CGRP-polypeptide (See page 22, line 27, page 46, agonists and antagonists, in particular) for treating allergies (abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the Calcitonin Gene-related peptide (CGRP) as taught by Cadieux *et al* with the CGRP receptor activity modifying protein such as analog CGRP-RCF or peptide fragment thereof as taught by the WO 98/03543 for a method to inhibit allergen-induced airway hyperresponsiveness in a mammal taught by Cadieux *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 98/03543 publication teaches the reference CGRP analog is useful for treating asthma and allergies (See abstract, in particular). Cadieux *et al* teach that CGRP acts a potent bronchoprotector agent on both guinea pig and human by limit the extend of airway hyperresponsiveness in inflamed airway such as asthma or ova sensitized lung (See page 242, column 1, 2nd paragraph, in particular).

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
April 19, 2004

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600